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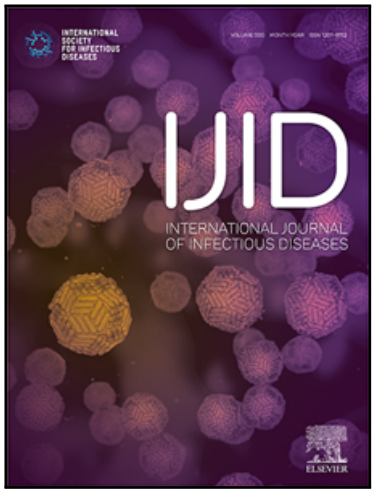

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HIGHLIGHTS

- SARS-CoV-2 induces long-lasting loss of enterocyte membrane integrity
- Elevated urinary I-FABP levels are associated with disease severity and poor outcome
- Damage to enterocytes is correlated to high IL-6 production

Clinical investigation of intestinal fatty acid-binding protein (I-FABP) as a biomarker of SARS-CoV-2 infection

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Short Title: Damage to enterocytes in SARS-CoV-2

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ABSTRACT

Objectives: SARS-CoV-2 exhibits tropism for the gastrointestinal tract, however lesions in enterocytes and their correlation with disease severity and patient prognosis are still unknown.

Methods: SARS-CoV-2 patients were enrolled in five medical centres in the São Paulo State, Brazil. Clinical characteristics and laboratory findings of patients were recorded. At admission, 7th and 14th day of hospitalisation, plasma and urine samples were collected. The levels of cytokines (IFN-γ, IL-6 and TNF-α) and the biomarker intestinal fatty acid-binding protein (I-FABP) were measured.

Results: COVID-19 patients displayed ≈48-, 74- and 125-fold increased urinary I-FABP levels at admission (n=283; p<0.001), 7th (n=142; p<0.01) and 14th day (n=75; p<0.01) of hospitalisation, respectively. Critically ill patients and nonsurvivors showed higher I-FABP concentrations compared to those in the infirmary and survivors, respectively, within the same hospital stay periods. At admission, infected patients demonstrated enhanced production of plasma IFN-γ and IL-6. The ROC curve suggested I-FABP as a biomarker for disease severity of COVID-19 at admission (p<0.0001; Youden index=6.89; AUC=0.699). Patients with I-FABP≥6.89 showed higher IL-6 and C-reactive protein levels (p<0.001) at admission, as well as prolonged length of hospital stay.

Conclusions: Our findings revealed damage to enterocytes in SARS-CoV-2 infection, which is associated to illness severity, poor prognosis and exacerbated inflammatory response.

Keywords: intestinal epithelial cells, cytokines, inflammation, COVID-19, interleukin-6.

SHORT COMMUNICATION

Gastrointestinal (GI) symptoms including vomiting, abdominal discomfort and diarrhoea have been reported in coronavirus infections at the onset of hospitalisation, affecting 10-30% of patients (Parasa et al., 2020). SARS-CoV-2 RNA has been detected in faeces and stomach, duodenum and colon biopsies (Lin et al., 2020; Zhao et al., 2020). COVID-19 patients with ongoing diarrhoea have displayed enhanced concentration of faecal calprotectin (a marker of gut inflammation), as well as systemic interleukin (IL)-6 production, regardless of the viral load (Effenberger et al., 2020). Although SARS-CoV-2 exhibits tropism for the GI tract, it remains unknown whether lesions in the intestinal epithelium occur.

Intestinal fatty acid-binding protein (I-FABP) is a cytosolic protein expressed in mature enterocytes of the small and large intestines (Pelsers et al., 2003). A basal level of urinary I-FABP represents the physiological turnover rate of the epithelium, whilst its increment may indicate enterocytes cell damage. In sepsis and IBD, the increased urinary concentration of I-FABP has been confirmed as a reliable biomarker and predictor of disease reactivation, worse prognosis and clinical complications (Ho et al., 2020). Therefore, our study assessed the levels of I-FABP in hospitalised patients with SARS-CoV-2 infection and investigated its role as a predictor of disease severity and poor prognosis.

This prospective cohort study enrolled 283 inpatients from five medical centres (Hospital das Clínicas, Hospital Santa Lydia, Hospital Unimed and Santa Casa de Misericórdia in Ribeirão Preto city and also Hospital e Maternidade Santa Isabel in Jaboticabal city), São Paulo State, Brazil (**Supplementary methods**). SARS-CoV-2 infection was confirmed through viral RNA detection in nasopharyngeal swabs by real-

time RT-PCR and the positive cases were recruited between April to September 2020. Comorbidities such as GI disorders (IBD, celiac disease and cancer), HIV, and alcohol and drugs addictions were exclusion criteria. At admission, 7th and 14th day of hospitalisation (at infirmary or intensive care unit), venous blood and urine samples were collected in the morning (0600-0800 AM), chilled and transferred to the research laboratory. Total blood and urine were centrifuged (1200 *g*, 15 min, 4 ºC), the supernatants aliquoted and kept at -70ºC for further analysis. Healthy volunteers were seronegative for the presence of anti-SARS-CoV-2 IgM and IgG antibodies.

I-FABP and cytokines (TNF-α, IFN-γ and IL-6) were quantified by ELISA, according to the manufacturer's instructions (R&D Systems, Minneapolis, MN, USA). Urinary data were normalised to creatinine concentrations (LabTest, Lagoa Santa, MG, Brazil). Continuous variables were expressed as median (interquartile range [IQR]) or 10-90 percentile range, and then compared using Mann-Whitney *U*-test or Kruskal-Wallis test (**Supplementary results**). Categorical variables were compared by Fisher's exact test or Pearson χ^2 test. Statistical significance was considered different when $p<0.05$.

Table 1 lists the demographic, clinical characteristics, and laboratory findings of SARS-CoV-2 patients (survivors and nonsurvivors) and healthy volunteers. Nonsurvivors showed higher number of underlying comorbidities (cardiovascular and pulmonary diseases, diabetes, degenerative and malignancies), as well as deviations of the laboratory parameters (anaemia, leucocytosis, lymphocytopenia, D-dimers, CRP, LDH, serum creatinine and urea), requirement of mechanic ventilation and intensive care at admission. At 7th and 14th day of hospitalisation, aging, pre-existing diseases, leucocytosis and need for mechanic ventilation were relevant factors in nonsurvivor patients.

Noteworthy, COVID-19 patients displayed ≈48-, 74- and 125-fold increased urinary I-FABP levels at admission, 7th and 14th day of hospitalisation, respectively (**Figure 1A**; p<0.001). Critically ill patients showed higher I-FABP concentrations compared to those in the infirmary within the same hospital stay periods (**Figure 1B**). Likewise, nonsurvivor patients were distinguished by increased I-FABP levels in contrast to survivors (**Figure 1C**). At admission, the inflammatory response was characterised by augmented plasma IFN-γ and IL-6 levels in SARS-CoV-2 patients (**Figure 1D**). Interestingly, urinary IL-6 concentrations were elevated in infected patients and nonsurvivors (**Figure 1E**). The ROC analysis indicated I-FABP as a good biomarker for disease severity, predictor for poor prognosis of COVID-19 at admission (**Figure 1F**; Youden index=6.89; p<0.0001) and prolonged hospital stay (**Figure 1G**). Patients with I-FABP≥6.89 ng/mg showed higher plasma and urine IL-6 and serum CRP concentrations, suggesting an interaction between inflammation and damage to enterocytes (**Figure 1G**).

Epithelial cells from ileum and colon express ACE2, the host cell entry receptor of coronaviruses, invading them for replication (Hoffmann et al., 2020) and shedding virions for several weeks after the onset of the illness (Zhao et al., 2020). Enteric symptoms reflect a break in the gut mucosa homeostasis, triggering the immune response and "cytokine release syndrome" (Effenberger et al., 2020). Soluble protein mediators, such as IFN-γ and IL-6, are key drivers of the inflammation-associated enterocyte damage and also responsible for increased gut mucosal permeability (Neurath, 2014; Wang et al., 2001). Indeed, our findings confirmed the detrimental contribution of SARS-CoV-2 to the loss of enterocyte membrane integrity, which is correlated with increased I-FABP levels (up to the 14th day after hospitalisation) and patient clinical condition. Moreover, patients whose I-FABP≥6.89 ng/mg also showed

exacerbated IL-6 production, which is a predictive cytokine of disease progression and ARDS complication (Santa Cruz et al., 2021). Our results revealed that increased I-FABP levels at admission may predict poor prognosis and SARS-CoV-2 illness severity, such as need for intensive care, mechanic ventilation and prolonged hospital stay.

Abbreviations list: ACE-2: angiotensin converting enzyme-2; ARDS: acute respiratory distress syndrome; AUC: area under curve; COVID-19: coronavirus disease of 2019; Cr: creatinine; CRP: C-reactive protein; ELISA: enzyme-linked immunosorbent assay; GI: gastrointestinal; HIV: human immunodeficiency virus; IBD: inflammatory bowel diseases; ICU: intensive care unit; IFN-γ: interferon-γ; Ig: immunoglobulin; IL: interleukin; ROC curve: receiver operating characteristic curve; RT-PCR: reverse transcriptase polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; TNF-α: tumor necrosis factor-α.

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Ethics approval: The study protocol was approved by the Research Ethics Committee of Clinics Hospital of Ribeirão Preto Medical School, University of São Paulo (protocol CAAE 30794820.7.0000.5440) and all patients or family members gave the informed consent to participate in this research.

Patient and public involvement: Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Contributors: Study concept and design: RSS, HG, FLS, ABF. Involved in the patient care: FLS, MAM, KMLM, AMD, MRC. Patient recruitment: RSS, HG, FLS, KJBP, MAM, AMD, MRC. Laboratory Analyses: RSS, HG. Data collection: RSS, HG, FLS, KJBP. Statistical analysis: RSS, ABF. Drafting the manuscript: RSS. All the authors edited the manuscript and have approved the final version.

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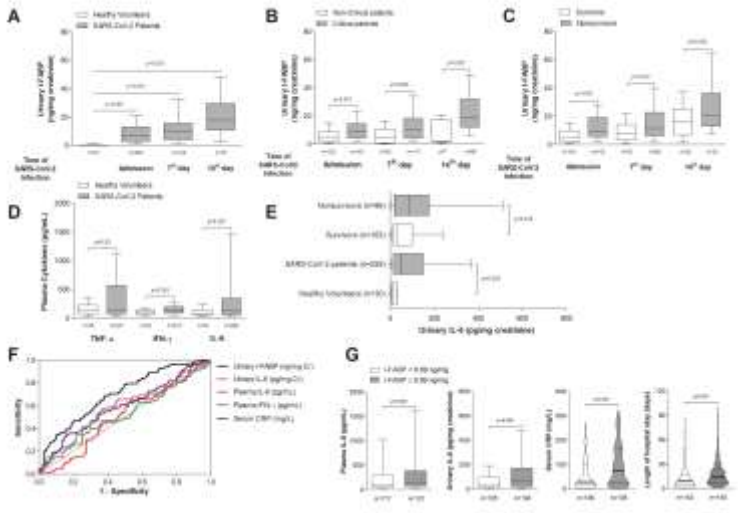

Figure 1. Urinary I-FABP as a prognostic biomarker of SARS-CoV-2 disease severity. (A) Urinary I-FABP concentration determined by ELISA in healthy volunteers and SARS-CoV-2 infected patients at admission, 7th and 14th day of hospitalisation (Kruskal-Wallis test and Dunn's multiple comparison post-test). **(B)** Urinary I-FABP concentration in SARS-CoV-2 patients in non-critical and critical clinical conditions at admission, 7th and 14th day of hospitalisation (Mann-Whitney test). **(C)** Urinary I-FABP concentration in SARS-CoV-2 survivor and nonsurvivor patients at admission, 7th and 14th day of hospitalisation (Mann-Whitney test). **(D)** Plasma cytokines levels of TNF-α, IFN-γ and IL-6 determined by ELISA at admission (Mann-Whitney test). **(E)** Urinary IL-6 concentration at admission in healthy volunteers, SARS-CoV-2 infected patients, survivors and nonsurvivors (Mann-Whitney test). **(F)** Comparison of ROC analysis of urinary I-FABP (AUC=0.699, 95% CI=0.636-0.762, p<0.0001), urinary IL-6 (AUC=0.573, 95% CI=0.476-0.671, p=0.14), plasma IL-6 (AUC=0.509, 95% CI=0.436-0.582, p=0.82), plasma IFN-γ (AUC=0.523, 95% CI=0.445-0.602, p=0.54) and serum CRP (AUC=0.591, 95% CI=0.519-0.662, p=0.01) for SARS-CoV-2 survivor and non-survivor patients. Cr: creatinine. **(G)** Plasma and urinary IL-6 concentrations, serum CRP levels at admission and length of hospital stay in SARS-CoV-2 infected

patients divided according to the Youden index=6.89 ng/mg creatinine (low I-FABP<6.89 and high I-FABP≥6.89 ng/mg) obtained from the ROC curve in **(F)** (Mann-Whitney test). Results shown as bars and violin plots are expressed as median and 10-90 interquartile range. *n* represents the number of patients per group. *P* values indicate the statistical significance between groups.

Table 1. Demographic, clinical characteristics and laboratory parameters of healthy volunteers and SARS-CoV-2 infected patients (Survivors and Nonsurvivors)

Parameters	Healthy Volunteers (*n*=37)	SARS-CoV-2 infected patients					
		Admission (*n*=283)		7th day (*n*=142)		14th day (*n*=75)	
		Survivors (*n*=181)	Nonsurvivors (*n*=102)	Survivors (*n*=76)	Nonsurvivors (*n*=66)	Survivors (*n*=42)	Nonsurvivors (*n*=33)
Gender M/F (%)	33/67 [γ]	60/40	52/48	57/43	51/49	67/33	48/52 [b]
Age, years [&]	55 [49-60] [α]	61 [50-71]	69 [62-77] [c]	62 [54-70]	68 [58-77] [b]	61 [53-70]	68 [58-77] [b]
Ethnicity (C/AA/H) (%)	87/8/5 [β]	70/15/15	80/16/4 [a]	75/18/7	86/2/12 [c]	74/12/14	85/1/14 [b]
BMI, kg/m^2 [&]	27.5 [24.5-30.3] [α]	30.5 [26.7-34.2]	28.7 [26.0-35.3]	31.5 [27.5-35.2]	29.0 [25.9-35.8]	29.8 [26.8-34.4]	28.9 [25.5-37.6]
MAP, mmHg [&]	90.0 [80.0-96.7]	93.3 [80.5-99.1]	88.0 [76.3-96.0]	91.0 [78.3-98.3]	87.0 [75.3-96.7]	91.0 [78.3-98.3]	88.5 [77.9-104.2]
HR, beats/min [&]	75 [69-79] [γ]	85 [73-92]	86 [77-98]	85 [76-96]	90 [79-98]	85 [76-96]	91 [83-104] [a]
Underlying Comorbidities, no. (%)							
Smoker/ex-smoker	0 (0) [γ]	29 (16.0)	31 (30.4) [b]	15 (19.7)	16 (24.2)	8 (19.0)	8 (24.2)
Arterial hypertension	10 (27.0) [γ]	99 (54.7)	74 (72.5) [b]	51 (67.1)	50 (75.6)	28 (66.7)	30 (90.9) [b]
Cardiovascular diseases	1 (2.7) [γ]	32 (17.7)	31 (30.4) [a]	18 (23.7)	22 (33.3)	11 (26.2)	10 (30.3)
Diabetes	2 (5.4) [γ]	61 (33.7)	50 (49.0) [a]	33 (43.4)	29 (43.9)	19 (45.2)	18 (54.5)
Pulmonary diseases	0 (0) [β]	9 (5.0)	15 (14.7) [b]	2 (2.6)	7 (10.6)	2 (4.8)	4 (12.1)
Chronic kidney diseases	0 (0)	7 (3.9)	9 (8.8)	2 (2.6)	5 (7.6)	0 (0)	4 (12.1) [a]
Thyroid disease	1 (2.7)	11 (6.1)	12 (11.8)	9 (11.8)	9 (13.6)	4 (9.5)	4 (12.1)
Dyslipidaemia	2 (5.4)	23 (12.7)	16 (15.7)	15 (19.7)	11 (16.7)	9 (21.4)	4 (12.1)
Degenerative disorders	0 (0) [γ]	1 (0.5)	9 (8.8) [c]	0 (0)	4 (6.1) [a]	0 (0)	0 (0)
Neurological diseases	1 (2.7)	12 (6.6)	6 (5.9)	8 (10.5)	7 (10.6)	5 (11.9)	4 (12.1)
Malignancies	0 (0) [γ]	2 (1.1)	15 (14.7) [c]	1 (1.3)	9 (13.6) [b]	1 (2.4)	6 (18.2) [a]
Other diseases	3 (8.1) [α]	8 (3.9)	13 (12.7) [a]	5 (6.6)	8 (12.1)	3 (7.1)	5 (15.2)

Haematological Indexes [&]							
Haemoglobin, g/dL	14.8 [14.0-15.2] [γ]	12.6 [11.3-14.0]	11.6 [10.0-13.3] [b]	11.7 [10.2-12.9]	10.0 [8.5-12.3] [c]	9.7 [8.7-11.3]	9.2 [8.2-11]
Erythrocytes, 10^6/µL	4.5 [4.42-4.90] [α]	4.3 [3.9-4.7]	4.2 [3.6-4.6]	4.0 [3.6-4.4]	3.67 [3.0-4.3] [b]	3.3 [2.9-3.8]	3.12 [2.74-3.69]
Leukocytes, 10^3/µL	5.38 [4.35-5.71] [γ]	8.2 [6.1-11.08]	11.4 [7.78-15.2] [c]	11.45 [8.23-16.03]	14.5 [10.2-23.2] [b]	10.2 [8.2-12.8]	12.6 [9.34-19.83] [a]
Neutrophils, 10^3/µL	2.65 [1.97-3.08] [γ]	6.01 [4.2-8.7]	8.89 [6.01-12.9] [c]	9.00 [6.0-12.4]	11.8 [7.45-19.85] [c]	7.8 [4.3-9.8]	10.75 [6.31-17.05] [a]
Monocytes, 10^3/µL	0.34 [0.27-0.38]	0.36 [0.22-0.54]	0.4 [0.27-0.68]	0.5 [0.3-0.7]	0.5 [0.31-0.8]	0.5 [0.3-0.8]	0.5 [0.3-0.8]
Lymphocytes, 10^3/µL	1.94 [1.47-2.17] [β]	1.1 [0.7-1.44]	0.89 [0.6-1.34] [a]	1.23 [0.71-1.79]	1.0 [0.6-1.59]	1.51 [1.0-2.1]	1.27 [0.93-1.82]
Platelets, 10^3/µL	209 [181-247]	230 [173-304]	230 [181-287]	271 [224-358]	250 [172-322] [a]	232 [165-304]	235 [143-327]
D-dimer, µg/mL [†]	< 0.5 [γ]	1.4 [0.59-3.25]	3.17 [1.84-6.84] [c]	2.31 [1.32-3.32]	2.61 [1.93-3.58]	2.51 [1.74-4.37]	3.4 [2.55-10.11] [a]
Biochemical Indexes [&]							
Glycaemia, mg/dL	78 [75-87] [γ]	155 [119-229]	168 [138-230]	170 [116-234]	176 [127-232]	142 [117-198]	133 [114-208]
CRP, mg/L	0.3 [0.2-0.4] [γ]	41.7 [16.7-109.3]	76.8 [20.1-163.3] [a]	21.3 [7.0-54.0]	33.6 [9.1-109.7]	67.0 [21.1-143.5]	53.5 [12.1-180.0]
ALT, U/L	20.4 [13.8-28.6] [γ]	45.5 [27.3-66.3]	39.5 [22.5-67.2]	61.0 [43.0-95.7]	58 [31.0-110.7]	66.0 [43.1-106.5]	57.1 [45.3-101.7]
AST, U/L	21.0 [19.0-27.0] [γ]	42.0 [30.0-65.9]	50.0 [29.0-71.2]	42.3 [31.0-55.3]	47.1 [33.0-86.0]	42.5 [29.0-69.5]	39.2 [34.9-111.5]
LDH, U/L	183.0 [172-189] [γ]	340.0 [263-466.4]	437.1 [293.6-675] [b]	345.0 [279-470]	408.3 [327.9-607] [b]	326.0 [259-401]	392.2 [285-571.9]
Serum creatinine, mg/dL	0.8 [0.7-0.9] [α]	1.0 [0.8-1.3]	1.43 [0.97-2.63] [c]	1.0 [0.8-1.5]	1.56 [1.01-2.87] [c]	1.1 [0.8-1.5]	1.66 [0.87-2.12] [a]
Serum urea, mg/dL	31.0 [28.0-38.0] [α]	45.0 [31.2-62.0]	74.9 [46.6-119.1] [c]	62.0 [40.0-99.9]	111.9 [56.2-167.8] [c]	62.0 [41.0-108.2]	102.6 [46.3-155.3] [a]
Respiratory Indexes [&]							
pH [†]	7.4 [7.35-7.45]	7.4 [7.32-7.44]	7.32 [7.23-7.40] [c]	7.4 [7.34-7.43]	7.34 [7.25-7.4]	7.4 [7.35-7.44]	7.33 [7.28-7.4]
PaO_2, mmHg [†]	90.0 [80-100]	83.9 [71.0-95.2]	78.4 [67.7-91.5]	72.5 [67.0-82.2]	75.4 [68.9-83.3]	73.4 [64.6-80.7]	73.0 [67.4-80.4]
$PaCO_2$, mmHg [†]	40.0 [35.0-45.0]	34.8 [27.8-45.0]	42.2 [34.0-48.6] [b]	44.1 [38.9-51.9]	45.4 [35.0-51.8]	38.4 [33.4-46.1]	42.5 [32.6-49.2]
SaO_2, % [†]	96.5 [95.0-98.0]	96.4 [93.8-97.1]	95.6 [92.3-97.1] [a]	96.4 [94.1-97.2]	95.7 [94.1-97.2]	96.0 [94.8-97.0]	95.5 [93.0-97.0]
Lactate, mmol/L [†]	1.25 [0.5-2.0]	2.0 [1.45-2.6]	2.0 [1.42-2.75]	1.89 [1.37-2.6]	1.77 [1.28-2.6]	1.80 [1.4-2.4]	1.51 [0.76-2.71]

Treatments, no. (%)							
Antibiotic therapy	-	132 (72.9)	102 (100.0) [c]	59 (77.6)	51 (77.3)	40 (95.2)	33 (100.0)
Antiviral therapy	-	25 (13.8)	12 (11.8)	2 (2.6)	1 (1.5)	0 (0)	0 (0)
Corticosteroids	-	123 (68.0)	81 (79.4) [a]	58 (76.3)	51 (77.3)	21 (50.0)	24 (72.7)
Anticoagulants	-	112 (61.9)	93 (91.2) [c]	75 (98.7)	55 (83.3) [c]	41 (97.6)	33 (100.0)
Hydroxychloroquine	-	12 (6.6)	4 (3.9)	3 (3.9)	3 (4.5)	0 (0)	0 (0)
Hospitalisation Characteristics							
Length of hospital stay (days)	-	11 [4-22]	13 [8-21] [a]	-	-	-	-
ICU length of stay (days)	-	0 [0-12]	11 [6-19] [c]	-	-	-	-
Severe/critical care type, no. (%) [#]	-	73 (40.3)	88 (86.3) [c]	54 (71.1)	63 (95.5) [c]	35 (83.3)	33 (100.0) [a]
Mechanic ventilation, no. (%)	-	60 (33.1)	73 (71.6) [c]	52 (68.4)	59 (89.4) [b]	28 (66.7)	33 (100.0) [c]

Legend: ALT (alanine aminotransferase); AST (aspartate aminotransferase); BMI (body mass index); CRP (C-reactive protein); Ethnicity (C = Caucasian, AA = Afro American, H = Hispanic); HR (heart rate); ICU (intensive care unit); LDH (lactate dehydrogenase); MAP (mean arterial pressure); $PaCO_2$ (partial pressure of carbon dioxide in arterial blood); PaO_2 (partial pressure of oxygen in arterial blood); SaO_2 (arterial oxygen saturation).

[&] Values expressed as median [interquartile range]

[†] Healthy volunteers with standardized reference values

[#] Severe/critical care type was defined as respiratory failure requiring mechanical ventilation and ICU admission

[α] $p<0.05$, [β] $p<0.01$ and [γ] $p<0.001$ vs. SARS-CoV-2 patients (survivors and nonsurvivors) at the admission

[a] $p<0.05$, [b] $p<0.01$ and [c] $p<0.001$ vs. survivors SARS-CoV-2 patients at the respective period of hospitalisation